CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074888

Trade Name : DESMOPRESSIN ACETATE INJECTION

Generic Name: Desmopressin Acetate Injection 4mcg/ml

Sponsor : Gensia Laboratories, Ltd.

Approval Date: October 15, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074888

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074888

APPROVAL LETTER

DN

ANDA 74-888

OCT 15 1997

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92618

Dear Mr. Harrigan:

This is in reference to your abbreviated new drug application dated April 17, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Desmopressin Acetate Injection, 4 mcg/mL.

Reference is also made to your amendments dated December 21, 1996; and July 18, August 5, August 22, September 8, and September 12, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined that your Desmopressin Acetate Injection, 4mcg/mL, is bioequivalent and, therefore, therapeutically equivalent, to the listed drug (DDAVP® Injection, 4 mcg/mL, of Rhone Poulenc Rorer Pharmaceuticals, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074888

FINAL PRINTED LABELING

Y36-202-302
Package Insert

GENSIA®
LABORATORIES, LTD.

APPROVED

Desmopressin Acetate Injection

DESCRIPTION

Desmopressin acetate injection is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Mol. Wt. 1183.2

Molecular Formula: $C_{48}H_{68}N_{14}O_{14}S_2 \cdot 3H_2O$

SCH_2CH_2CO-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot C_2H_4O_2 \cdot 3H_2O$

1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

Desmopressin acetate injection is provided as a sterile, aqueous solution for intravenous or subcutaneous injection.

Each mL provides:	
Desmopressin acetate	4 mcg
Sodium chloride	9 mg
Hydrochloric acid	to adjust pH to 3.5-5

Both the 1 mL and the 10 mL vials contain chlorobutanol as a preservative (5 mg/mL).

CLINICAL PHARMACOLOGY

Desmopressin acetate injection contains as active substance, 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin, a synthetic analogue of the natural hormone arginine vasopressin. One mL (4 mcg) of desmopressin acetate solution has an antidiuretic activity of about 16 IU; 1 mcg of desmopressin acetate is equivalent to 4 IU.

Desmopressin acetate has been shown to be more potent than arginine vasopressin in increasing plasma levels of factor VIII activity in patients with hemophilia and von Willebrand's disease Type I.

Dose-response studies were performed in healthy persons, using doses of 0.1 to 0.4 mcg/kg body weight, infused over a 10-minute period. Maximal dose response occurred at 0.3 to 0.4 mcg/kg. The response to desmopressin acetate of factor VIII activity and plasminogen activator is dose-related, with maximal plasma levels of 300 to 400 percent of initial concentrations obtained after infusion of 0.4 mcg/kg body weight. The increase is rapid and evident within 30 minutes, reaching a maximum at a point ranging from 90 minutes to two hours. The factor VIII related antigen and ristocetin cofactor activity were also increased to a smaller degree, but still are dose-dependent.

1. The biphasic half-lives of desmopressin were 7.8 and 75.5 minutes for the fast and slow phases, respectively, compared with 2.5 and 14.5 minutes for lysine vasopressin, another form of the hormone. As a result, desmopressin acetate provides a prompt onset of antidiuretic action with a long duration after each administration.

2. The change in structure of arginine vasopressin to desmopressin acetate has resulted in a decreased vasopressor action and decreased actions on visceral smooth muscle relative to the enhanced antidiuretic activity, so that clinically effective antidiuretic doses are usually below threshold levels for effects on vascular or visceral smooth muscle.

3. When administered by injection, desmopressin acetate has an antidiuretic effect about ten times that of an equivalent dose administered intranasally.

4. The bioavailability of the subcutaneous route of administration was determined qualitatively using urine output data. The exact fraction of drug absorbed by that route of administration has not been quantitatively determined.

5. The percentage increase of factor VIII levels in patients with mild hemophilia A and von Willebrand's disease was not significantly different from that observed in normal, healthy individuals when treated with 0.3 mcg/kg of desmopressin acetate infused over ten minutes.

6. Plasminogen activator activity increases rapidly after desmopressin acetate infusion, but there has been no clinically significant fibrinolysis in patients treated with desmopressin acetate.

7. The effect of repeated desmopressin acetate administration when doses were given every 12 to 24 hours has generally shown a gradual diminution of the factor VIII activity increase noted with a single dose. The initial response is reproducible in any particular patient if there are 2 or 3 days between administrations.

INDICATIONS AND USAGE

Hemophilia A

Desmopressin acetate injection is indicated for patients with hemophilia A with factor VIII coagulant activity levels greater than 5%.

Desmopressin acetate will often maintain hemostasis in patients with hemophilia A during surgical procedures and postoperatively when administered 30 minutes prior to scheduled procedure.

Desmopressin acetate will also stop bleeding in hemophilia A patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

Desmopressin acetate is not indicated for the treatment of hemophilia A with factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have factor VIII antibodies.

In certain clinical situations, it may be justified to try desmopressin acetate in patients with factor VIII levels between 2%-5%; however, these patients should be carefully monitored.

von Willebrand's Disease (Type I)

Desmopressin acetate injection is indicated for patients with mild to moderate classic von Willebrand's disease (Type I) with factor VIII levels greater than 5%. desmopressin acetate will often maintain hemostasis in patients with mild to moderate von Willebrand's disease during surgical procedures and postoperatively when administered 30 minutes prior to the scheduled procedure.

Desmopressin acetate will usually stop bleeding in mild to moderate von Willebrand's patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

Those von Willebrand's disease patients who are least likely to respond are those with severe homozygous von Willebrand's disease with factor VIII coagulant activity and factor VIII von Willebrand factor antigen levels less than 1%. Other patients may respond in a variable fashion depending on the type of molecular defect they have. Bleeding time and factor VIII coagulant activity, ristocetin cofactor activity, and von Willebrand factor antigen should be checked during administration of desmopressin acetate to ensure that adequate levels are being achieved.

Desmopressin acetate is not indicated for the treatment of severe classic von Willebrand's disease (Type I) and when there is evidence of an abnormal molecular form of factor VIII antigen. See **WARNINGS**.

Diabetes Insipidus

Desmopressin acetate injection is indicated as antidiuretic replacement therapy in the management of central (cranial) diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. Desmopressin acetate is ineffective for the treatment of nephrogenic diabetes insipidus.

Desmopressin acetate is also available as an intranasal preparation. However, this means of delivery can be compromised by a variety of factors that can make nasal insufflation ineffective or inappropriate. These include poor intranasal absorption, nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as transsphenoidal hypophysectomy, create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

CONTRAINDICATION

Desmopressin acetate injection is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate injection.

WARNINGS

Patients who do not have need of antidiuretic hormone for its antidiuretic effect, in particular those who are young or elderly, should be cautioned to ingest only enough fluid to satisfy thirst in order to decrease the potential occurrence of water intoxication and hyponatremia.

Fluid intake should be adjusted downward, particularly in very young and elderly patients, in order to decrease the potential occurrence of water intoxication and hyponatremia.

Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma.

Desmopressin acetate should not be used to treat patients with Type IIB von Willebrand's disease since platelet aggregation may be induced.

PRECAUTIONS

GENERAL: For injection use only.

Desmopressin acetate injection has infrequently produced changes in blood pressure causing either a slight elevation in blood pressure or a transient fall in blood pressure and a compensatory increase in heart rate. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease.

Desmopressin acetate injection should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.

There have been rare reports of thrombotic events following **desmopressin acetate injection** in patients predisposed to thrombus formation. No causality has been determined; however, the drug should be used with caution in these patients.

Severe allergic reactions have been reported rarely. Fatal anaphylaxis has been reported in one patient who received intravenous desmopressin acetate. It is not known whether antibodies to **desmopressin acetate injection** are produced after repeated injections.

Hemophilia A

Laboratory tests for assessing patient status include levels of factor VIII coagulant, factor VIII antigen, and factor VIII ristocetin cofactor (von Willebrand factor) as well as activated partial thromboplastin time. Factor VIII coagulant activity should be determined before giving desmopressin acetate for hemostasis. If factor VIII coagulant activity is present at less than 5% of normal, desmopressin acetate should not be relied on.

von Willebrand's Disease

Laboratory tests for assessing patient status include levels of factor VIII coagulant activity, factor VIII ristocetin cofactor activity, and factor VIII von Willebrand factor antigen. The skin bleeding time may be helpful in following these patients.

Diabetes Insipidus

Laboratory tests for monitoring the patient include urine volume and osmolality. In some cases, plasma osmolality may be required.

DRUG INTERACTIONS: Although the pressor activity of desmopressin acetate is very low compared with the antidiuretic activity, use of doses as large as 0.3 mcg/kg of desmopressin acetate with other pressor agents should be done only with careful patient monitoring.

Desmopressin acetate has been used with epsilon aminocaproic acid without adverse effects.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There have been no long-term studies in animals to assess the carcinogenic, mutagenic, or impairment of fertility potential of desmopressin acetate.

PREGNANCY. Teratogenic Effects. Pregnancy Category B: Reproduction studies performed in rats and rabbits by the subcutaneous route at doses up to 10 mcg/kg/day have revealed no

evidence of harm to the fetus due to desmopressin acetate. This dose is equivalent to 10 times (for Factor VIII stimulation) or 38 times (for diabetes inspidius) the systemic human dose based on mg/m^2 surface area.

There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, there are no adequate and well-controlled studies in pregnant women. Published reports stress that, as opposed to preparations containing the natural hormones, Desmopressin acetate in antidiuretic doses has no uterotonic action; but the physician will have to weigh possible therapeutic advantages against possible danger in each case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assayable desmopressin in breast milk following an intranasal dose of 10 mcg. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to a nursing woman.

PEDIATRIC USE: Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. *Desmopressin acetate injection should not be used in infants younger than three months* in the treatment of hemophilia A or von Willebrand's disease; safety and effectiveness in children under 12 years of age with diabetes insipidus have not been established.

ADVERSE REACTIONS

Infrequently, desmopressin acetate has produced transient headache, nausea, mild abdominal cramps, and vulval pain. These symptoms disappeared with reduction in dosage. Occasionally, injection of desmopressin acetate has produced local erythema, swelling, or burning pain. Occasional facial flushing has been reported with the administration of desmopressin acetate. **Desmopressin acetate injection** has infrequently produced changes in blood pressure causing either a slight elevation or a transient fall and a compensatory increase in heart rate. Severe allergic reactions including anaphylaxis have been reported rarely with **desmopressin acetate injection**.

See **WARNINGS** for the possibility of water intoxication and hyponatremia.

There have been rare reports of thrombotic events (acute cerebrovascular thrombosis, acute myocardial infarction) following **desmopressin acetate injection** in patients predisposed to thrombus formation.

OVERDOSAGE

See **ADVERSE REACTIONS** above. In case of overdosage, the dosage should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition.

There is no known specific antidote for desmopressin acetate.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Hemophilia A and von Willebrand's Disease (Type I)

Desmopressin acetate injection is administered as an intravenous infusion at a dose of 0.3 mcg desmopressin acetate/kg body weight diluted in sterile physiological saline and infused slowly over 15 to 30 minutes. In adults and children weighing more than 10 kg, 50 mL of diluent is used; in children weighing 10 kg or less, 10 mL of diluent is used. Blood pressure and pulse should be monitored during infusion. If **desmopressin acetate injection** is used preoperatively, it should be administered 30 minutes prior to the scheduled procedure.

The necessity for repeat administration of desmopressin acetate or use of any blood products for hemostasis should be determined by laboratory response as well as the clinical condition of the patient. The tendency toward tachyphylaxis (lessening of response) with repeated administration given more frequently than every 48 hours should be considered in treating each patient.

Diabetes Insipidus

This formulation is administered subcutaneously or by direct intravenous injection. **Desmopressin acetate injection** dosage must be determined for each patient and adjusted accordingly to the pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover.

The usual dosage range in adults is 0.5 mL (2 mcg) to 1 mL (4 mcg) daily, administered intravenously or subcutaneously, usually in two divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For patients who have been controlled on intranasal desmopressin acetate and who must be switched to the injection form, either because of poor intranasal absorption or because of the need for surgery, the comparable antidiuretic dose of the injection is about one-tenth the intranasal dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Desmopressin acetate injection is available as a sterile solution as follows:

NDC Number	**Desmopressin Acetate Injection**	**Volume**
0703-**5051-03**	4 mcg/mL	1 mL preserved vial
0703-**5054-01**	4 mcg/mL	10 mL multiple dose vial

1 mL vials are packaged 10 unit cartons per shelf pack.

10 mL vials are packaged in single unit cartons.

Keep refrigerated at about 4°C (39°F).

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

August 1997
Gensia Laboratories, Ltd.
Irvine CA 92618

REFRIGERATE

GENSIA LABORATORIES, LTD.

NDC 0703-**5051-01**

Desmopressin Acetate Injection 4 mcg/mL

For IV or SC Use
1 mL Preserved Vial

Each mL provides:

Desmopressin Acetate .....4 mcg
Chlorobutanol.....5 mg
Sodium Chloride...9 mg
Hydrochloric acid to adjust pH to 3.5-5.

Usual Dosage: See package insert for dosage information.

Keep refrigerated at 4°C (39°F).

GENSIA LABORATORIES, LTD.

NDC 0703-**5051-01**

Desmopressin Acetate Injection 4 mcg/mL

For IV or SC Use
1 mL Preserved Vial

See bottom panel for lot number and expiration date.
Caution: Federal (USA) law prohibits dispensing without prescription.
Gensia Laboratories, Ltd., Irvine CA 92618 X12-505-101

+H6745051010 23

REFRIGERATE

GENSIA®
LABORATORIES, LTD.

NDC 0703-**5054-01**

Desmopressin Acetate Injection 4 mcg/mL

For IV or SC Use
10 mL Multiple Dose Vial

Each mL provides:
Desmopressin
Acetate .....4 mcg
Chlorobutanol.....5 mg
Sodium Chloride...9 mg
Hydrochloric acid to adjust pH to 3.5-5.

Usual Dosage: See package insert for dosage information.

Keep refrigerated at 4°C (39°F).

GENSIA®
LABORATORIES, LTD.

NDC 0703-**5054-01**

Desmopressin Acetate Injection 4 mcg/mL

For IV or SC Use
10 mL Multiple Dose Vial

See bottom panel for lot number and expiration date.
Caution: Federal (USA) law prohibits dispensing without prescription.
Gensia Laboratories, Ltd., Irvine CA 92618 X12-505-401

+H674505401026

REFRIGERATE

GENSIA®
LABORATORIES, LTD.

NDC 0703-**5054-01**

Desmopressin Acetate Injection 4 mcg/mL

For IV or SC Use
10 mL Multiple Dose Vial

Each mL provides:
Desmopressin
Acetate .....4 mcg
Chlorobutanol.....5 mg
Sodium Chloride...9 mg
Hydrochloric acid to adjust pH to 3.5-5.

Usual Dosage: See package insert for dosage information.

Keep refrigerated at 4°C (39°F).

GENSIA®
LABORATORIES, LTD.

NDC 0703-**5054-01**

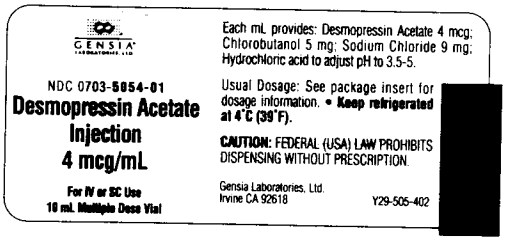
Desmopressin Acetate Injection 4 mcg/mL

For IV or SC Use
10 mL Multiple Dose Vial

See bottom panel for lot number and expiration date.
Caution: Federal (USA) law prohibits dispensing without prescription.
Gensia Laboratories, Ltd., Irvine CA 92618 X12-505-401

+H674505401026

Vial Label/Shelf Pack A Label - NDC #0703-5054-01
(Part #Y29-505-402)
10 mL Multiple Dose Vial



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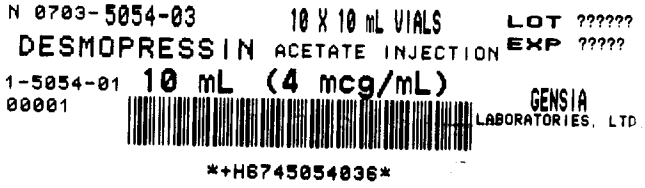

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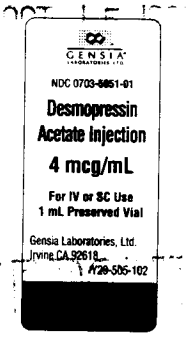
(Part #Y29-505-102)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074888

CHEMISTRY REVIEW(S)

DW

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 74-888

3. NAME AND ADDRESS OF APPLICANT

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718-1902

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Desmopressin Acetate

13. DOSAGE FORM
Injection Solution

14. STRENGTH
4 µg/mL

10. PHARMACOLOGICAL CATEGORY
Desmopressin Acetate Injection is an antidiuretic hormone affecting renal water conservation. It increases plasma levels of Factor VIII activity in patients with hemophilia and von Willebrand's disease Type I.

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION
The applicant's product is the generic version of DDAVP® Injection manufactured by Rhone-Poulenc Rorer Pharmaceuticals, Inc., NDA 18-938. There is no unexpired patent or exclusivity.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

04/17/96 The original ANDA was submitted.
11/20/96 NA major letter.
12/21/96 Amendment in response to letter of 11/20/96.
07/18/97 Labeling amendment in response to discussion with Jerry Phillips re chlorobutanol and packaging configurations on 6/25/97.
08/05/97 COMIS shows this as a chemistry amendment, but it was only microbiology. Ken Muhvich completed the assignment on 08-AUG-97, **so it should be closed out for chemistry.**
08/12/97 NA facsimile.
08/22/97 Response to NA facsimiles. This is chemistry and labeling only. **Therefore this assignment should be closed out for microbiology.**
09/08/97 Telephone chemistry amendment re finished product specifications.

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

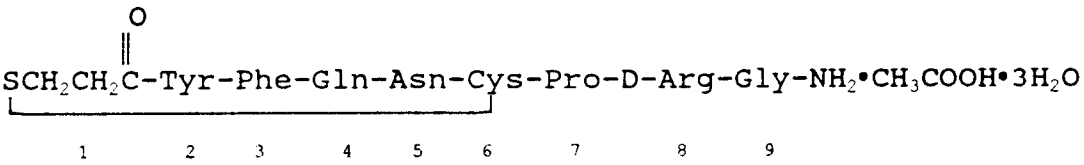
(b)5 - Gov't Pre-Decisional

15. CHEMICAL NAME AND STRUCTURE

$C_{48}H_{68}N_{14}O_{14}S_2 \cdot 3H_2O$. 1183.32 *CAS-62357-86-2*

Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine, monoacetate (salt), trihydrate;

1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate (salt) trihydrate.



16. RECORDS AND REPORTS N/A

17. COMMENTS

The review of ANDA 74-888 is **incomplete** in the following Point:

31. SAMPLES AND RESULTS

Neither the DS nor the DP is in the USP, so MV was requested on 8/4/97. In the amendment of 8/22/97, Gensia acknowledges that aproval of ANDA 74-888 is contingent upon acceptable MV. Gensia commits to cooperate with the Agency to resolve any MV issues.

The following Points **have been completed** for ANDA 74-888:

25. MANUFACTURING AND PRECESSING

The sterilization validation was found satisfactory per review of Ken Muhvich, Ph.D. on 8/8/97.

32. LABELING

Container, carton, and insert labeling were approved by L. D. Golson on 9/3/97.

33. ESTABLISHMENT INSPECTION

The facilities were found to be **acceptable** on 10/21/96.

34. BIOEQUIVALENCE STATUS

The Bio waiver was **granted** by J. S. Kharidia on 7/25/96.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 74-888 can be **APPROVED** pending acceptable MV or the passing of 30 days, whichever comes sooner.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 9/9/97

Endorsed by P.Schwartz, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074888

BIOEQUIVALENCE REVIEW(S)

ANDA 74-888

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes.
Irvine CA 92718

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Desmopressin Acetate Injection, 4 mcg/mL.

> The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 25 1996

Desmopressin Acetate Injection
4 mcg/ml; 1 mL per ampule
4 mcg/ml; 10 mL per vial
ANDA # 74-888
Reviewer: Jahnavi S. Kharidia
x:\jsk\74888w.s96

Gensia Laboratories, Ltd.
19 Hughes
Irvine, CA 92718
Submission Date:
April 17, 1996

Review of a Waiver

Introduction:

Desmopressin Acetate is an antidiuretic hormone affecting renal water conservation and is a synthetic analogue of 8-arginine vasopressin. The reference product is DDAVP® injection manufactured by Rhone-Poulenc Rorer, 4 mcg/mL in 1 mL per ampule and 10 mL per vial.

Objective:

The firm is requesting a waiver of the *in vivo* bioequivalence study requirements for its test products, Desmopressin Acetate Injection; 4 mcg/mL in 1 mL per ampule and 10 mL per vial under the provisions of CFR 314.92.

Formulations:

The comparative formulation of the test and the reference products are listed below.

Ingredients	Amount (per mL)	
	Test	**Reference**
Desmopressin Acetate	4.0 mcg	4.0 mcg
Chlorobutanol Hemihydrate	5.25 mg*	5.0 mg+
Sodium Chloride	9.0 mg	9.0 mg
Hydrochloric Acid, NF	to adjust pH	to adjust pH
Water for Injection, USP	q.s.	q.s.

* 5.25 mg of chlorobutanol hemihydrate = 5 mg chlorobutanol
\+ Provided in 10 mL multiple dose vial only.

Comments:

1. The test drug product, Desmopressin Acetate (4.0 mcg/mL; 1mL ampule and 10 mL vial) is a parenteral drug product intended for administration by injection.

2. The test product contains the same active and inactive ingredients, dosage form, strength, route of administration and conditions of use as the listed reference product, DDAVP®; with the exception of the addition of chlorobutanol as a preservative for the single dose formulation. The innovator's DDAVP® 1 mL ampule is preservative free.

3. As per the interim inactive ingredients policy, preservative comes under the category of exception excipient for parenterals. A qualitative difference in exception excipient can be accepted provided that such an excipient has previously been approved and its amount is not greater than maximum concentration used for same route of administration.

4. The innovator's DDAVP® 10 mL vial contains chlorobutanol as a preservative in the same concentration (5 mg/ml) as the test product.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Gensia Laboratories, Ltd. demonstrates that Desmopressin Acetate Injection, 4 mcg/ml, 1 mL and 10 mL vials falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of *in vivo* bioavailability study be granted. The test products, Desmopressin Acetate Injection, 4 mcg/mL, 1 mL and 10 mL vials, are deemed bioequivalent to the currently approved DDAVP® injection manufactured by Rhone-Poulenc Rorer.

The firm should be informed of the above recommendation.

/S/

J. S. Kharidia, Ph.D.
Division of Bioequivalence
Review Branch III

RD Initialed R.M. Mhatre
FT Initialed R.M. Mhatre /S/ Date: 7/18/96

Ramakant M. Mhatre, Ph.D.
Chief, Branch III